REMARKS

Upon entry of this amendment, Claims 1-37, 39, 40, 42-63, and 65 constitute the pending claims in the present application. Among them, Claims 1-27, 47, 56-62, and 65 are directed to non-elected inventions and are withdrawn from further consideration. Applicants will cancel these claims upon indication of allowable subject matter as appropriate.

The other claims are canceled without prejudice. Applicants reserve the right to prosecute claims of identical or similar scope in future continuing applications.

Applicants thank the Examiner for withdrawing the claim objections and rejections based on 35 U.S.C. 112, second paragraph, and 35 U.S.C. 102.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim Rejection under 35 U.S.C. § 103

Claims 54 and 55 remains rejected for allegedly being obvious over Keenan et al. (of record) as evidenced by Amara et al. (of record) in view of Mehta (of record).

As Applicants have previously argued, the combined teachings of these references fail to teach or suggest the screening methods of Claim 28; moreover, Keenan teaches away from the claimed PEG linker for the reasons of record.

The Examiner deemed the "teach away" argument unpersuasive, "because use of the linkers results in some effect which would result in a predictable outcome in the claimed assay."

Applicants respectfully disagree. Although the PEG linker was not completely ineffective in Keenan's assay, it is nonetheless a "poor" one, as the Examiner apparently agrees. Indeed, Keenan – who surely qualifies as a person skilled in this field – highlights the "dramatic difference" in effectiveness, supporting the idea that the limited activity of the PEG linkers is *materially low* compared to the other linkers tested. Thus, based on this result, the "predictable outcome" as viewed by one of skill in the art, is that a ligand with the PEG linker may have minimal (if any) activity in the claimed method. The Examiner has provided no reason that one

of ordinary skill in the art would fail to be deterred by Keenan's admonitions. Under these circumstances, it can hardly be said that a person of skill in the art would be motivated to use such "poor" technology in future endeavors, given that a wide array of more reliable and linkers well known for this purpose in the art. Accordingly, Applicants submit that a prima facie case of obviousness cannot be made under these circumstances.

Moreover, even if a prima facie case of obviousness were properly made, Applicants have found that such linkers unexpectedly are much more effective than Keenan's results suggest. Applicants have surprisingly found that the use of PEG linkers in accordance with the present invention does not yield a "poor" result, as one of skill in the art would have predicted in view of Keenan. In contrast, the PEG linker actually increases the cellular uptake of the hybrid ligands, as shown in Figures 6 and 7 and Example 7 of the specification.

Specifically, in Example 7, yeast cell growth depends on the ability of a ligand (added to the liquid growth medium) to dimerize a DNA-binding polypeptide and a transcription activator. Applicants first demonstrated that a ligand having the subject PEG linker, Mtx-(ethylenglycol)$_3$-Dex (GPC 285937), is much easier to get into the yeast cells than Mtx-mdbt-Dex, a similar ligand with a different linker (used in Lin et al., J. Am. Chem. Soc. 2000, 122:4247-8). As a result, yeast cells grew better in the presence of GPC 285937 as compared to Mtx-mdbt-Dex.

Similar results were obtained as shown in Figure 6, where a halo assay (instead of liquid medium growth) was used to compare Mtx-mdbt-Dex with GPC 285937.

Furthermore, data in Figure 7 shows that a hybrid ligand of the invention (GPC 285937) showed significant improvement over the prior art hybrid ligand (Mtx-mdbt-Dex) under conditions appropriate to library screening of yeast cells. Under those conditions, growth of individual yeast colonies on SD-media with Mtx-mdbt-Dex was hardly detectable, whereas clones visibly grew better on media containing GPC 285937.

In contrast, Keenan compares many "hydrophobic" linkers side-to-side with the subject PEG linker. Keenan's data clearly show that the hydrophobic linkers work well in the Keenan assay, while the PEG linker works very "poorly." This makes Applicants' finding even more

surprising, in that the PEG linker works very well in the subject methods, while the hydrophobic linker (such as Mtx-mdbt-Dex) works very poorly.

Moreover, solubility is hardly the only reason a person skilled in the art would have been dissuaded from using a PEG linker as recited in the pending claims. Keenan discusses, from the last line, page 1313 to page 1314, that flexibility of a $(PEG)_5$ linker and a PEG-like linker compared to those of some non-PEG variants may account for the "dramatic difference in activities." In other words, Keenan attributes the "poor" assay results of the PEG linkers to its flexibility, and implies that less flexibility is better for a linker.

The flexibility issue is echoed in page 10622 of Amara: "[a] dimerizer with a long linker led to very poor activation, suggesting that a minimum proximity or rigidity between the proteins may be required ... Activity then increased as linkers shortened." (emphasis added). Again, Amara also teaches that "very poor" activity is associated with "flexible" linkers (such as the PEG linker), and Amara explicitly *teaches away* by recommending using short and rigid linkers to increase dimerization activity. In contrast, the instant claimed invention is directed to the use of relatively long and flexible PEG linkers, such as those with 2-25 repeats (see, for example, Claims 28 and 34). Such PEG linkers are indeed very flexible, because they comprise only single bonds, which are free to rotate, and are linear, lacking substituents that might tend to favor particular confirmations and restrict free rotation about these bonds.

Applicants submit that this is yet another reason why the claimed invention is non-obvious in view of the prior art, which plainly teaches away from the use of PEG linkers as claimed. This argument also applies to all other obviousness rejections raised by the Examiner (addressed below).

These surprising results were not predictable based on the prior art teaching (such as those in Keenan and Bertozzi), and thus show that the claimed invention would have been non-obvious to a person skilled in the art in view of the prior art at the time of filing. Applicants do not understand how the instant Final Office Action can characterize this unexpected result as a "predictable outcome" despite Keenan, and respectfully request the Examiner to provide a more detailed explanation.

Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 43-45 are rejected for allegedly being obvious in view of Johnsson *et al.* (U.S. Pat. No. 5,585,245, cited as reference P04 on the IDS filed 4/26/2003; entire reference) in view of Licitra *et al.* (*P.N.A.S. U.S.A.* **93**: 12817-12821, 1996, "Licitra") and Bertozzi (or record) as evidenced by Varshavsky *et al.* (*P.N.A.S. U.S.A.* **93**: 12142-12149, 1996, "Varshavsky").

Applicants respectfully disagree.

In the previous response, Applicants argued that the PEG linked structures are non-obvious over any possible combinations of the art cited against other claims, because Licitra *teaches away* from improving the linker in its hybrid ligand, instead suggesting that a better approach would be to "generate yeast strains that are more permeable without significantly affecting yeast viability" (*see* page 12820, middle of the right column). In addition, both Keenan (*supra*) and Bertozzi (*infra*) teach away from using the PEG linkers. The Examiner apparently has not considered this argument.

Pursuant to MPEP 2143.01: "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (C.C.P.A., 1959)."

Applicants submit that combining Licitra with Bertozzi would have changed the principle of operation for Licitra, which calls for the generation of "yeast strains that are more permeable without significantly affecting yeast viability." One of skill in the art, in view of the results in Keenan and Bertozzi, would have predicted that the PEG linker-containing ligand is not suitable for use with Licitra, since the ligand with this linker would be expected to be hydrophilic and thus not very membrane-permeable. As discussed above, this turns out not in fact to be the case for the recited ligands, which are surprisingly very membrane-permeable – further evidence of the non-obviousness of the claimed subject matter.

Therefore, Claims 43-45 as amended are non-obvious over the cited art. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner also maintains all the obviousness rejections based on the combination of Liu (of record) in view of Bertozzi. The Examiner also maintains the rejection based on the combination of Liu and Holt (of record). Applicants respectfully disagree and address these rejections together below since they involve a common issue.

In the "Response to Arguments" section, the Examiner states that Applicants' response "essentially asserts that Bertozzi teaches away from the combination, because Bertozzi teaches that PEG linkers are water-soluble, and the linked compounds would have increased water solubility (hydrophilicity), which would be less likely to be membrane permeable." The Examiner found this argument unpersuasive, "because the method of Liu et al. does not require the compounds to be capable of crossing the cell membrane. Liu et al. teach that the hybrid ligand is introduced into the cell by traversing the membrane, or by electroporation or any permeation procedure that is known in the art (e.g., column 7, lines 3-15). Thus the hybrid ligand is not required to be hydrophobic to be used in the method of Liu et al."

However, as discussed above, contrary to the reasonable expectations of those of skill in the art at the time of filing, Applicants have found that PEG-linked hybrid ligands have excellent membrane permeability. This unexpected result, which renders the recited hybrid ligands surprisingly effective in the claimed methods, is clear evidence that the claimed methods are not, in fact, obvious.

Thus, the disclosure in Liu regarding electroporation and "other methods" in fact support Applicants' argument that the claimed invention is non-obvious in light of unexpected membrane permeability property of the PEG-linked hybrid ligands. Reconsideration and withdrawal of the rejection are respectfully requested.

Further regarding the obviousness rejection based on the combination of Liu and Holt, Applicants have previously made two distinct arguments in traversing this rejection. One of the arguments is based on the unexpected membrane permeability property of the PEG-linker-containing ligand, which, as argued above, supports the non-obviousness of using the PEG linker in the claimed methods.

The other argument is based on the failure of Holt to render a species obvious where the prior art reference Holt only discloses a broad genus (e.g., Holt only generically suggests that the linker L "need not contain essential elements for binding to the immunophilin proteins, and may be selected from a very broad range of structural types" (emphasis added, see page 2, lines 22-23 of Holt)). Although Holt provides a cell-based transfection assay in pages 48-49, there does not appear to be relevant teaching in Holt as to *which* of the numerous types of linkers are preferred for *any* reason. Moreover, there is nothing in Holt that would lead one to predict the unexpected results Applicants have achieved using the recited ligands with their particular linking moiety.

Furthermore, Holt generically discloses that the two ligand moieties can be independently selected (i.e., can be homo- or hetero-dimeric), though few if any heterodimeric compounds are disclosed. The claimed invention is a novel selection invention (distinct from the generic Holt disclosure) of a PEG linker AND a heterodimeric compound. Applicants submit that Holt does not actually specifically exemplify any heterodimeric hybrid ligand, and certainly not one with a PEG linker.

The Examiner has not specifically responded to this argument Applicants made; thus Applicants respectfully request the Examiner to reconsider this argument together with the arguments presented herein, and withdrawal the obviousness rejection based on Liu and Holt.

Finally, Applicants note that under the new Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103, effective on October 10, 2007, the Examiner must first act as a fact finder to resolve the Graham factual inquiries, including: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art.

Applicants note that in each and every rejection maintained, the Examiner has pre-assumed without any explanation or discussion that the level of skill for one of ordinary skill in the relevant art is "high." Applicants respectively disagree with the Examiner's unsubstantiated conclusive statement that the level of skill is "high." Applicants submit that a full recitation of the grounds upon which this level of skill was selected is critical to Applicants' ability to

ascertain the propriety of this assignment, and by not having properly and openly resolved the level of skill in the art, the Examiner has failed to follow the new Examination Guidelines for Determining Obviousness, and could not have had properly reached the legal conclusion that the claimed invention is obvious over the prior art based on the Graham factors. Therefore, reconsideration and withdrawal of the obviousness rejections are respectfully requested.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**, under Order No. **DFMP-P01-018**.

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Respectfully submitted,

By_____

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